# TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

Attorney Docket No. 01198

U.S. Application No. (if known, see 37 CFR 1.5)
09/926534

| INTERNATIONAL APPLICATION NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIMED |
|---|---|---|
| PCT/FR00/01365 | May 19, 2000 | May 19, 1999 |

TITLE OF INVENTION
PHARMACEUTICAL COMPOSITIONS FOR ORAL ADMINISTRATION OF PHLOROGLUCINOL AND PREPARATION THEREOF

APPLICANT(S) FOR DO/EO/US
Abderrahim Bennis, Jean-Jacques Serrand and Farid Bennis

Applicant herewith submits to the United States Designated Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3).
   a. ☐ are transmitted herewith (only if not required by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5).

**Items 11 to 16 below concern document(s) or information included:**

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ As assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
    Application Data Sheet

23338
PATENT TRADEMARK OFFICE

| 17. ☒ The following fees are submitted: | CALCULATIONS | PTO USE ONLY |
|---|---|---|
| **BASIC NATIONAL FEE (37 CFR 1.492 (a)(1)-(5):** | | |
| Neither international preliminary examination fee (37 CFR 1.482) Nor international search fee (37 CFR 1.445(a)(2) paid to USPTO And International Search Report not prepared by EPO or JPO..... $1,040.00 | | |
| International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by EPO or JPO.....$890.00 | | |
| International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International search fee (37 CFR 1.445(a)(2)) paid to USPTO..... $740.00 | | |
| International preliminary examination fee paid to USPTO (37 CFR 1.482) But all claims did not satisfy provisions of PCT Article 33(1)-(4).....$710.00 | | |
| International preliminary examination fee paid to USPTO (37 CFR 1.482) And all claims satisfied provisions of PCT Article 33(1)-(4)..... $100.00 | | |
| **ENTER APPROPRIATE BASIC FEE AMOUNT =** | $890.00 | |
| Surcharge of **$130.00** for furnishing oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e). | $130.00 | |

| CLAIMS | NUMBER FILED | NUMBER EXTRA | RATE | | |
|---|---|---|---|---|---|
| Total Claims | 10 -20= | | X $18.00 | $ | |
| Independent Claims | 1 -3= | | X $84.00 | $ | |
| MULTIPLE DEPENDENT CLAIM(S) (if applicable) | | | | $ | |
| **TOTAL OF ABOVE CALCULATIONS =** | | | | $1020.00 | |
| Reduction of ½ for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28). | | | | $ | |
| **SUBTOTAL =** | | | | $1020.00 | |
| Processing fee of **$130.00** for furnishing English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f). | | | | $ | |
| **TOTAL NATIONAL FEE =** | | | | $1020.00 | |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). | | | | $ | |
| **TOTAL FEES ENCLOSED =** | | | | $1020.00 | |
| | | | | Amount to be refunded: | $ |
| | | | | charged: | $ |

a. ☐ A check in the amount of $ to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 04-0753 in the amount of $ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☐ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 04-0753. A duplicate copy of this sheet is enclosed.

d. ☒ A payment of $ 1020.00 is made by credit card. A Credit Card Payment Form (PTO-2038) is attached hereto. The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 CFR 1.16 or any patent application processing fees under 37 CFR 1.17, or credit any over payment to the credit card account shown on the attached Credit Card Payment Form. Refund of all amounts overpaid, including those of twenty-five dollars or less, is specifically requested. Any fees not accepted by the credit card shown on Form PTO-2038 may be charged to Deposit Account No. 04-0753.

SEND ALL CORRESPONDENCE TO:
Dennison, Scheiner & Schultz
612 Crystal Square 4
1745 Jefferson Davis Highway
Arlington, VA 22202-3417
Telephone (703) 412-1155 Ext. 23
Facsimile (703) 412-1161

SIGNATURE

Ira J. Schultz
NAME

28666
REGISTRATION NUMBER

Dkt. 01198

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the Application of: Group Art Unit:

ABDERRAHIM BENNIS et al Examiner:

Serial No.: US National Phase of
PCT/FR00/01365

Filed: concurrently herewith

For: PHARMACEUTICAL COMPOSITIONS FOR ORAL ADMINISTRATION OF PHLOROGLUCINOL AND PREPARATION THEREOF

**PRELIMINARY AMENDMENT AND INFORMATION DISCLOSURE STATEMENT**

Honorable Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Before calculation of the filing fee, please amend the above-identified application as follows:

**IN THE SPECIFICATION:**

Page 5, lines 15-16:

Group [A] C: Lyoc: 28% (not significant relative to the controls (Group B))

Group [C] A: Effervescent compound: 47% (significant at p > 0.001)

**IN THE CLAIMS:**

Please amend the claims as set forth hereinbelow and in the attached appendix:

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612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

1. (Amended) Pharmaceutical composition for oral administration of phloroglucinol, comprising, in a liquid state, a system which buffers the composition to a pH of between 3 and 7, or in a solid state, a system which, when placed in an aqueous medium, is capable of providing a buffer effect between pH 3 and pH 7.

2. (Amended) Pharmaceutical composition according to claim 1, wherein said buffer pH is between 4 and 6.

3. (Amended) Pharmaceutical composition according to claim 1, in the form of solutions, suspensions or syrups or in the form of tablets, gelatin capsules, powders, granules or lyophilizates.

4. (Amended) Pharmaceutical composition according to claim 1, wherein said system responsible for the buffer effect comprises at least one organic acid and/or at least one salt of an organic acid in association with at least one strong base and/or at least one salt of a strong base.

5. (Amended) Pharmaceutical composition according to claim 4, wherein said organic acid is selected from the group consisting of citric, tartaric, malic, lactic, acetic, glutaric, benzoic and adipic acids.

6. (Amended) Pharmaceutical composition according to claim 4, wherein said base comprises sodium bicarbonate, sodium carbonate, calcium carbonate, magnesium carbonate,



LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1185

sodium hydroxide, potassium hydroxide, potassium bicarbonate or potassium carbonate.

7. (Amended) Pharmaceutical composition according to claim 1, in the form of an effervescent solid galenical preparation.

8. (Amended) Pharmaceutical composition according to claim 1, in the form of an effervescent tablet.

9. (Amended) Pharmaceutical composition according to claim 1, in the form of an effervescent tablet containing citric acid and sodium bicarbonate.

10. (Amended) Process for the preparation of a pharmaceutical composition according to claim 1, comprising formulating the phloroglucinol in a liquid form with a system which buffers said liquid form to a pH of between 3 and 7, or in a solid form with a system which, when said solid form is placed in an aqueous medium, is capable of providing a buffer effect between pH 3 and pH 7.

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

**REMARKS**

The specification has been amended to correct a typographical error. As the effervescent tablet is described at page 5, lines 5-7 of the specification as "Group A" and the solution prepared from Lyoc is described at page 5, lines 9-11 as "Group C" the amendment at page 5, lines 15-16 is in accordance with the previous disclosure, and no new matter has been added.

The claims have been amended to delete all multiple dependencies, and to generally place the claims in better form for US practice.

Attached is the search report of the corresponding PCT application, together with copies of the references cited therein, which are listed on the attached Form PTO-1449.

Respectfully submitted,

Ira J. Schultz
Registration No. 28666

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

## APPENDIX

**IN THE SPECIFICATION:**

Page 5, lines 15-16:

Group [A] C: Lyoc: 28% (not significant relative to the controls (Group B))

Group [C] A: Effervescent compound: 47% (significant at p > 0.001)

**IN THE CLAIMS:**

1. (Amended) Pharmaceutical [compositions] composition for [the] oral administration of phloroglucinol, [characterized in that, when liquid, they contain] comprising, in a liquid state, a system which buffers [them] the composition to a pH of between 3 and 7, or [in that, when solid, they contain] in a solid state, a system which, when [they are] placed in an aqueous medium, is capable of [exerting] providing a buffer effect between pH 3 and pH 7.

2. (Amended) Pharmaceutical [compositions] composition according to claim 1, [characterized in that] wherein said buffer pH is between 4 and 6.

3. (Amended) Pharmaceutical [compositions] composition according to claim 1 [or 2], [characterized in that they are presented] in the form of solutions, suspensions or syrups or in the form of tablets, gelatin capsules, powders, granules or lyophilizates.



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DENNISON, SCHEINER, SCHULTZ & WAKEMAN
812 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

4. (Amended) Pharmaceutical [compositions] composition according to [any one of claims 1 to 3, characterized in that] claim 1, wherein said system responsible for the buffer effect comprises at least one organic acid and/or at least one salt of an organic acid in association with at least one strong base and/or at least one salt of a strong base.

5. (Amended) Pharmaceutical [compositions] composition according to claim 4, [characterized in that] wherein said organic acid is selected from the group consisting of citric, tartaric, malic, lactic, acetic, glutaric, benzoic and adipic acids.

6. (Amended) Pharmaceutical [compositions] composition according to claim 4 [or 5], [characterized in that] wherein said base [takes the form of] comprises sodium bicarbonate, sodium carbonate, calcium carbonate, magnesium carbonate, sodium hydroxide, potassium hydroxide, potassium bicarbonate or potassium carbonate.

7. (Amended) Pharmaceutical [compositions] composition according to [any one of claims 1 to 6, characterized in that they are presented] claim 1, in the form of an effervescent solid galenical [preparations] preparation.

8. (Amended) Pharmaceutical [compositions] composition according to [any one of claims 1 to 7, characterized in that they are presented] claim 1, in the form of an effervescent

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DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
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[tablets] tablet.

9. (Amended) Pharmaceutical [compositions] composition according to [any one of claims 1 to 7, characterized in that they are presented] claim 1, in the form of an effervescent [tablets] tablet containing citric acid and sodium bicarbonate.

10. (Amended) Process for the preparation of a pharmaceutical [compositions] composition according to [any one of the preceding claims, characterized in that it comprises] claim 1, comprising formulating the phloroglucinol in [the] a liquid form with a system which buffers said liquid form to a pH of between 3 and 7, or in [the] a solid form with a system which, when said solid form is placed in an aqueous medium, is capable of [exerting] providing a buffer effect between pH 3 and pH 7.

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DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

Pharmaceutical compositions for oral administration of phloroglucinol and preparation thereof

The present invention relates to pharmaceutical compositions for the oral administration of phloroglucinol (1,3,5-trihydroxybenzene) and to the preparation thereof. Said compositions, which are novel, are of value inasmuch as the antispasmodic activity of the phloroglucinol (antispasmodic activity on the smooth muscle fibers) is potentiated in these compositions.

Said antispasmodic activity of said phloroglucinol has been known since 1961 (reference may be made in particular to Debray et al., THERAPIE, 1961, 16, pages 978 to 990, and Cahen et al., THERAPIE, 1962, page 17). Thus phloroglucinol is used in the treatment of spasmodic and painful manifestations of the urinary tract, the hepatic ducts, the digestive tract and the gynecological apparatus. At the present time, it is administered orally in the form of tablets or lyophilizates, rectally in the form of suppositories, or by injection (i.m. or i.v.). Lyophilizates are generally preferred for oral administration inasmuch as they exhibit a more rapid and more complete bioavailability than tablets. Said lyophilizates are active more rapidly. The customary oral dose of phloroglucinol is generally 160 mg, taken as two tablets or lyophilizates.

In such a context, the Applicant now proposes a novel galenical form for the oral administration of said phloroglucinol. Said novel galenical form can come in a number of variants. It can be novel *per se* (cf., for example, the effervescent tablets, granules or powders described further in the present text) or it can consist of a modified conventional galenical form (cf., for example, the tablets or lyophilizates described further in the present text). Whatever its form of presentation, said galenical form is characteristically buffered to a pH of between 3 and 7.

According to its main subject, the present invention thus relates to pharmaceutical compositions for the oral administration of phloroglucinol, characterized in that, when liquid, they contain a system which buffers them to a pH of between 3 and 7, or in that, when solid, they contain a system which, when they are placed in an aqueous medium, is capable of exerting a buffer effect between pH 3 and pH 7.

The composition of the pharmaceutical compositions of the invention is characteristically such that it exerts a buffer effect in the pH range mentioned

above, said range being delimited by said values pH 3 and pH 7 inclusive. Said buffer effect in said pH range ($3 \leq pH \leq 7$) is of course compatible with the stability of the active principle in question, namely phloroglucinol (this compound, which is oxidizable in alkaline media, must not in fact be exposed to pH values of >7); it makes it possible to reduce the gastric acidity and, totally surprisingly, it potentiates the antispasmodic activity of said phloroglucinol. Effervescent tablets buffered as defined by the invention have thus proved almost as effective as an intramuscular injection, and oral lyophilizates buffered as defined by the invention have also proved more effective than the oral lyophilizates of the prior art (non-buffered).

Advantageously, the pharmaceutical compositions of the invention are buffered to a pH of between 4 and 6 ($4 \leq pH \leq 6$).

It has already been seen above that said pharmaceutical compositions, buffered as defined by the invention, can exist in various forms. In particular, they can be presented in liquid forms (directly buffered to an appropriate pH) such as solutions, suspensions or syrups, or in solid forms (which will develop the buffer effect in a liquid, generally water, when they are taken, or in the stomach after they have been taken) such as tablets (effervescent or non-effervescent, advantageously effervescent, cf. below), gelatin capsules, powders (effervescent or non-effervescent, advantageously effervescent, cf. below), granules (effervescent or non-effervescent, advantageously effervescent, cf. below) or lyophilizates. This is not an exhaustive list.

Those skilled in the art who are specialized in galenics will in any case know how to formulate phloroglucinol, especially in one or other of the unit forms listed above, with an appropriate system responsible for the desired buffer effect. Such unit forms (for example tablets, especially conventional tablets, double-core tablets, effervescent tablets) obviously and advantageously constitute the essence of the pharmaceutical compositions of the invention. However, pharmaceutical compositions containing at least two separate components (on the one hand a component containing at least the active principle, and on the other hand another component containing at least the system generating the desired buffer effect), said separate components being intended for simultaneous administration, cannot be totally excluded from the framework of the invention.

Within the framework of a preferred embodiment of the invention, said system responsible for the buffer effect comprises at least one organic acid and/or

at least one salt of an organic acid in association with at least one strong base and/or at least one salt of a strong base.

Within the framework of this preferred embodiment, said organic acid is advantageously selected from citric, tartaric, malic, lactic, acetic, glutaric, benzoic and adipic acids and/or said base takes the form of sodium bicarbonate, sodium carbonate, calcium carbonate, magnesium carbonate, sodium hydroxide, potassium hydroxide, potassium bicarbonate or potassium carbonate.

Particularly advantageously, the pharmaceutical compositions of the invention consist of effervescent solid galenical forms; they are presented especially in the form of effervescent tablets, effervescent granules or effervescent powders. Within the framework of this advantageous variant, the same system is generally and opportunely responsible for the desired buffer effect and the effervescence.

According to the invention, effervescent phloroglucinol tablets are very particularly preferred. Such tablets have proved more effective than the oral lyophilizates of the prior art and, in addition, they are less expensive to manufacture than said oral lyophilizates.

Such tablets are capable of containing the above-defined associations of organic acid(s) and/or organic acid salt(s) with strong base(s) and/or strong base salt(s). Advantageously, they contain the combination citric acid/sodium bicarbonate.

It is therefore to the inventors' credit to have established that the above-specified buffer effect potentiates the antispasmodic activity of phloroglucinol and to propose novel galenical forms of said phloroglucinol with potentiated antispasmodic activity, especially effervescent forms.

The preparation of the pharmaceutical compositions of the invention, as described above, constitutes the second subject of said invention. Said preparation is that of a buffered galenical form. Characteristically, it comprises formulating the phloroglucinol in the liquid form with a system which buffers said liquid form to a pH of between 3 and 7 (advantageously of between 4 and 6), or in the solid form with a system which, when said solid form is placed in an aqueous medium, is capable of exerting a buffer effect between pH 3 and pH 7 (advantageously between pH 4 and pH 6).

It has already been indicated that said preparation should not present any problems whatsoever for those skilled in the art who are specialized in galenics.

On a point of information, it is proposed to specify below, purely by way of illustration, an advantageous procedure for the preparation of effervescent phloroglucinol tablets.

First of all, the active principle, phloroglucinol dihydrate, is mixed with the system responsible for both the effervescence and the desired buffer effect, namely citric acid + sodium bicarbonate. Small amounts of additives, such as a lubricant (for example sodium benzoate) and/or a preservative and/or a sweetener (for example sucrose sodium), etc., are advantageously added to said mixture.

The resulting mixture of powders is sieved and then granulated with an aqueous-alcoholic solvent. The granules obtained are successively dried and graded. Their residual moisture content is then checked. Finally, they are lubricated and then compressed for agglomeration into tablet form. Said tablets are then packed in their primary packaging.

This process for the manufacture of effervescent tablets is not novel *per se*. The novelty derives from the fact that it is carried out with phloroglucinol.

Purely by way of illustration, the composition by weight of an effervescent tablet of the invention can also be specified below:

| | |
|---|---|
| Phloroglucinol (dihydrate) | 80.0 mg |
| Citric acid | 297.2 mg |
| Sodium bicarbonate | 362.6 mg |
| Sodium benzoate | 15.2 mg |

When dissolved in a glass of water, such a tablet generates a solution buffered to pH 4.5.

Finally, it is proposed to illustrate the value of the present invention by means of the following presentation of comparative results of pharmacological tests.

In said tests, the antispasmodic activity of different galenical forms of phloroglucinol was evaluated using the SIEGMUND test. The principle of this test, which is familiar to those skilled in the art, is summarized below.

The pain syndrome caused in mice by the intraperitoneal injection of 0.25 ml of a phenylbenzoquinone solution is characterized by stretching movements of the back paws and twisting movements of the dorso-abdominal musculature, which are counted over a period of 30 min, starting 15 min after the administration of said phenylbenzoquinone. An antispasmodic effect is represented by a reduction in the number of these movements. For each test, the

test substance is administered intragastrically, or by some other route, 30 min before the administration of said phenylbenzoquinone.

· A first study was performed on three groups of mice.

An effervescent tablet of the invention, containing 80 mg of phloroglucinol, was dissolved in distilled water so that a dose of 100 mg/kg was administered in a volume of 20 ml/kg via an esophageal tube (Group A of the invention).

The controls (Group B) received the same volume of distilled water.

An aqueous solution containing the same dose was prepared from oral lyophilizates (Lyoc) of the prior art. It was administered under the same conditions (Group C).

The results obtained were expressed as the percentage protection against the spasms induced by phenylbenzoquinone, relative to the controls. They are indicated below:

Group A: Lyoc: 28% (not significant relative to the controls (Group B))

Group C: Effervescent compound: 47% (significant at $p > 0.001$)

The antispasmodic activity exhibited by the effervescent tablet is appreciably greater than that of the oral lyophilizate.

· Under similar and obviously comparative conditions, said percentage inhibition of the spasms relative to a control group was evaluated at different doses (40 mg/kg, 80 mg/kg and 160 mg/kg) of phloroglucinol (dihydrate) formulated as:

- an oral lyophilizate: LYOC (prior art)
- an injectable solution: I.M. (prior art)
- an effervescent tablet: EFFERV. (invention)
- a buffered oral lyophilizate: LYOC′ (invention)

In this fourth case, a device was in fact implemented. A lyophilizate of the prior art (LYOC) was dissolved in distilled water and buffered to pH 5 with citric acid and sodium bicarbonate (LYOC′).

The results obtained are expressed as above in the following Table:

| | Percentage inhibition of spasms | | |
|---|---|---|---|
| | 40 mg/kg | 80 mg/kg | 160 mg/kg |
| LYOC | 6 | 24 | 34* |
| I.M. | 12 | 43*** | 59*** |
| EFFERV. | 20 | 43*** | 53*** |
| LYOC′ | | | 45*** |

* p = 0.05 *** p = 0.001

A statistical analysis performed between LYOC and I.M. or EFFERV. at the 80 mg dose shows a highly significant difference: p = 0.001.

A statistical analysis performed between LYOC and I.M. or EFFERV. at the 160 mg dose shows a highly significant difference: p = 0.01.

A statistical analysis performed between I.M. and EFFERV. at the 160 mg dose shows that the difference is not significant.

A statistical analysis performed between LYOC and LYOC′ at the 160 mg dose shows a statistically significant difference: p = 0.05.

A statistical analysis performed between EFFERV. and LYOC′ at the 160 mg dose shows that the difference is not significant.

The data in said Table leave no doubt as to the value of the present invention.

## Claims

1. Pharmaceutical compositions for the oral administration of phloroglucinol, characterized in that, when liquid, they contain a system which buffers them to a pH of between 3 and 7, or in that, when solid, they contain a system which, when they are placed in an aqueous medium, is capable of exerting a buffer effect between pH 3 and pH 7.

2. Pharmaceutical compositions according to claim 1, characterized in that said buffer pH is between 4 and 6.

3. Pharmaceutical compositions according to claim 1 or 2, characterized in that they are presented in the form of solutions, suspensions or syrups or in the form of tablets, gelatin capsules, powders, granules or lyophilizates.

4. Pharmaceutical compositions according to any one of claims 1 to 3, characterized in that said system responsible for the buffer effect comprises at least one organic acid and/or at least one salt of an organic acid in association with at least one strong base and/or at least one salt of a strong base.

5. Pharmaceutical compositions according to claim 4, characterized in that said organic acid is selected from citric, tartaric, malic, lactic, acetic, glutaric, benzoic and adipic acids.

6. Pharmaceutical compositions according to claim 4 or 5, characterized in that said base takes the form of sodium bicarbonate, sodium carbonate, calcium carbonate, magnesium carbonate, sodium hydroxide, potassium hydroxide, potassium bicarbonate or potassium carbonate.

7. Pharmaceutical compositions according to any one of claims 1 to 6, characterized in that they are presented in the form of effervescent solid galenical preparations.

8. Pharmaceutical compositions according to any one of claims 1 to 7, characterized in that they are presented in the form of effervescent tablets.

9. Pharmaceutical compositions according to any one of claims 1 to 7, characterized in that they are presented in the form of effervescent tablets containing citric acid and sodium bicarbonate.

10. Process for the preparation of pharmaceutical compositions according to any one of the preceding claims, characterized in that it comprises formulating the phloroglucinol in the liquid form with a system which buffers said liquid form to a pH of between 3 and 7, or in the solid form with a system which, when said solid

form is placed in an aqueous medium, is capable of exerting a buffer effect between pH 3 and pH 7.

Usa Provisoire 1

# DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

Docket No. _____

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled PHARMACEUTICAL COMPOSITIONS FOR ORAL ADMINISTRATION OF PHLOROGLUCINOL AND PREPARATION THEREOF

specification of which

(check one) __X__ is described and claimed in PCT International Application PCT/FR00/01365
filed on (MM/DD/YYYY) MAY 19, 2000 amended on _____
(if applicable)
(OR) _____ is described in United States Application Number _____
filed on (MM/DD/YYYY) _____ (OR) _____ is attached hereto.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Claimed? Yes | No |
|---|---|---|---|---|
| 99 06325 | FRANCE | MAY 19, 1999 | X | |
| | | | | |

I hereby claim the benefit under 35 U.S.C. 119(e) of any Unites States Provisional Application(s) listed below.

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I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) , or 365(c) of any PCT International application designating the Unites States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

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As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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| Donald L. Dennison | Reg. No. 19920 | Ira J. Schultz | Reg. No. 28666 |
| Burton Scheiner | Reg. No. 24018 | Scott T. Wakeman | Reg. No. 37750 |

DIRECT ALL CORRESPONDENCE TO: DENNISON, SCHEINER, SCHULTZ & WAKEMAN

DIRECT TELEPHONE CALLS TO:

Full name of sole or first inventor BENNIS Farid
(First, Middle, Family Name or Surname)

Inventor's signature _____ Date 04 JANUARY 2002

Residence CASABLANCA - MOROCCO Citizenship Moroccan
(City, State, Country)

Full Post Office Address 74 rue du Corail Paranfa - CASABLANCA - MOROCCO -

Full name of second joint inventor _____
(First, Middle, Family Name or Surname)

Second inventor's signature _____ Date _____

Residence _____ Citizenship _____
(City, State, Country)